

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-87. (Canceled)

88. (New) A mitochondrially targeted antioxidant compound, comprising:

a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and

a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the lipophilic cationic moiety, the linking moiety or the antioxidant moiety, wherein the antioxidant compound accumulates within mitochondria of an intact cell, and wherein at least one of the linking moiety, the lipophilic cationic moiety and the antioxidant moiety is selected such that within mitochondria the antioxidant moiety resides at a desired location within said mitochondria.

89. (New) The compound of claim 88 wherein the desired location is selected from the group consisting of an outer mitochondrial membrane, a mitochondrial intermembrane space, an inner mitochondrial membrane and a mitochondrial matrix.

90. (New) A mitochondrially targeted antioxidant compound, comprising:

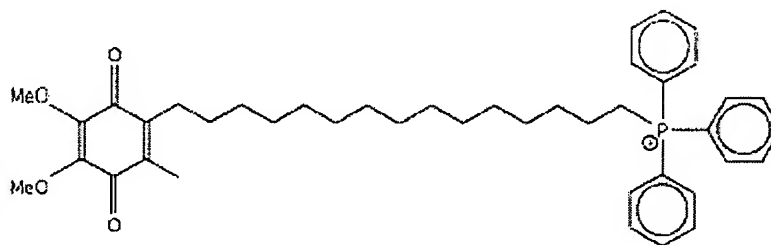
a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and

a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the lipophilic cationic moiety, the linking moiety or the antioxidant moiety, wherein the antioxidant compound accumulates within mitochondria of an intact cell, and wherein within said mitochondria the antioxidant moiety is at a distance from the lipophilic cationic moiety of between about 5 Angstroms and about 60 Angstroms.

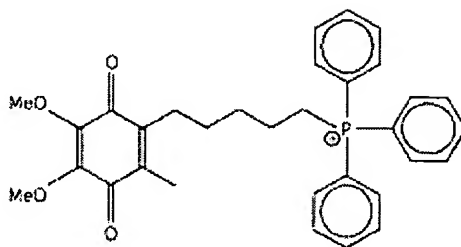
91. (New) The compound of claim 90 wherein the antioxidant moiety is at a distance from the lipophilic cationic moiety that is selected from the group consisting of (i) a distance of between about 10 angstroms and about 50 angstroms, (ii) a distance of between about 20 angstroms and about 40 angstroms, and (iii) a distance of between about 25 angstroms and about 35 angstroms.

92. (New) The compound of claim 90 wherein the linking moiety is selected from the group consisting of (i) a carbon chain having from about 1 to about 30 carbon atoms, (ii) a carbon chain having from about 2 to about 20 carbon atoms, (iii) a carbon chain having from about 2 to about 15 carbon atoms, (iv) a carbon chain having from about 3 to about 10 carbon atoms, and (v) a carbon chain having from about 3 to about 6 carbon atoms.

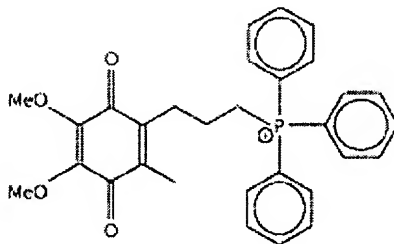
93. (New) A compound according to claim 90 which comprises at least one formula selected from the group consisting of:



I,



II, and



III.

94. (New) A mitochondrially targeted antioxidant compound, comprising:

a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and

a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the lipophilic cationic moiety, the linking moiety or the antioxidant moiety, wherein the antioxidant compound has a partition coefficient of less than about 20 in octanol:water and accumulates within mitochondria of an intact cell.

95. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the lipophilic cationic moiety comprises a cation that is selected from the group consisting of a triphenylphosphonium cation, a tribenzylammonium cation and a phosphonium cation.

96. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the salt forming anion comprises an alkyl sulfonate or an aryl sulfonate.

97. (New) The antioxidant compound of claim 96 wherein the alkyl sulfonate or aryl sulfonate is selected from the group consisting of methanesulfonate, ethanesulfonate, propanesulfonate, benzene sulfonate, *p*-toluene sulfonate and 2-naphthylene sulfonate.

98. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the salt forming anion comprises methanesulfonate.

99. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the salt forming anion comprises a non-nucleophilic anion that is selected from the group consisting of hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, tetra(perfluorophenyl)borate and trifluoromethane sulfonate.

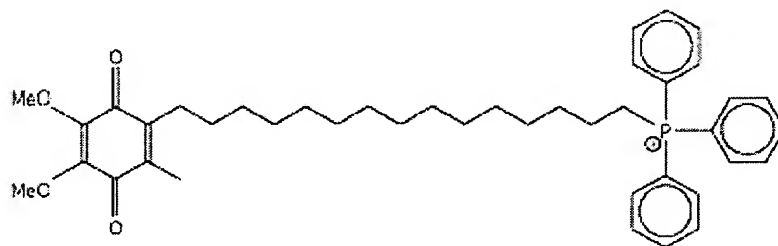
100. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the antioxidant moiety comprises a quinone or a quinol.

101. (New) The antioxidant compound of any one of claims 88, 90 and 94 wherein the antioxidant moiety is capable of interacting with a mitochondrial reductant to obtain or regain antioxidant activity.

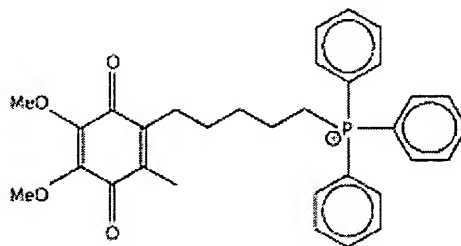
102. (New) The antioxidant compound of claim 101 wherein the mitochondrial reductant comprises mitochondrial Complex II.

103. (New) A pharmaceutical composition comprising an antioxidant compound according to any one of claims 88, 90 and 94; and a carrier or excipient.

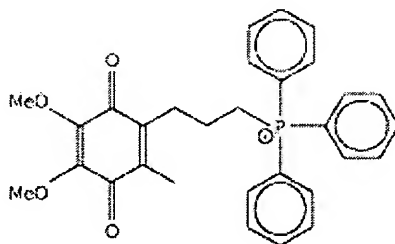
104. (New) The pharmaceutical composition according to claim 103 wherein the antioxidant compound comprises a compound which comprises a formula that is selected from the group consisting of:



I,

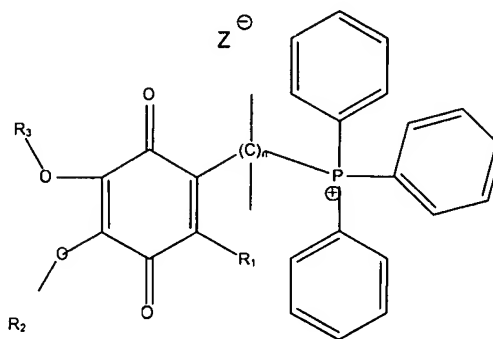


II, and



III.

105. (New) An antioxidant compound according to claim 94 which comprises a structure of the following formula:



or its quinol form, wherein R_1 , R_2 , and R_3 , are the same or different and are selected from C_1 to C_5 alkyl, substituted C_1 to C_5 alkyl and H, and wherein n is an integer from 2 to 20, and wherein Z is the salt forming anion.

106. (New) A pharmaceutical composition comprising an antioxidant compound according to claim 105; and a carrier or excipient.

107. (New) The pharmaceutical composition according to claim 103 which comprises cyclodextrin.

108. (New) The pharmaceutical composition of claim 107 wherein the antioxidant compound and cyclodextrin are present at a compound-to-cyclodextrin molar ratio that is from about 10:1 to about 1:10.

109. (New) The pharmaceutical composition of claim 107 wherein the antioxidant compound and cyclodextrin are present at a compound-to-cyclodextrin molar ratio that is selected from the group consisting of (i) from about 5:1 to about 1:5, (ii) from about 4:1 to about 1:4, (iii) from about 2:1 to about 1:2, (iv) about 1:1 and (v) about 1:2.

110. (New) A method of reducing oxidative stress in a cell, comprising:
contacting a cell that comprises mitochondria with an antioxidant compound that comprises an antioxidant compound according to claim 105.

111. (New) A method of reducing oxidative stress in a cell, comprising:
contacting a cell that comprises mitochondria with an antioxidant compound that comprises at least one antioxidant compound that is selected from the group consisting of an antioxidant compound according to claim 88, an antioxidant compound according to claim 90, and an antioxidant compound according to claim 94.

112. (New) A method of therapy or prophylaxis of a patient who would benefit from reduced oxidative stress, comprising administering to said patient a therapeutically efficacious dose of a pharmaceutical composition which comprises (i) an antioxidant compound that comprises at least one antioxidant compound that is selected from the group consisting of an antioxidant compound according to claim 88, an antioxidant compound according to claim 90, and an antioxidant compound according to claim 94, and (ii) a carrier or excipient.

113. (New) A method of screening for a mitochondrially localizing amphiphilic antioxidant compound, comprising:

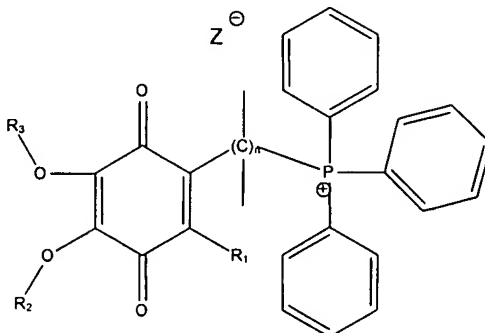
(a) administering a candidate amphiphilic antioxidant compound to a mitochondrial preparation comprising deenergized mitochondria, to determine binding of the compound to mitochondria that substantially lack a mitochondrial membrane potential;

(b) energizing the mitochondria of (a) to determine mitochondrial uptake of the candidate amphiphilic antioxidant compound in the presence of a mitochondrial membrane potential;

(c) deenergizing the mitochondria to abolish the membrane potential;
and

(d) determining mitochondrial release of the candidate amphiphilic antioxidant compound in the absence of the mitochondrial membrane potential, wherein incomplete release of said compound indicates mitochondrial localization.

114. (New) A method for synthesizing a compound of the formula I



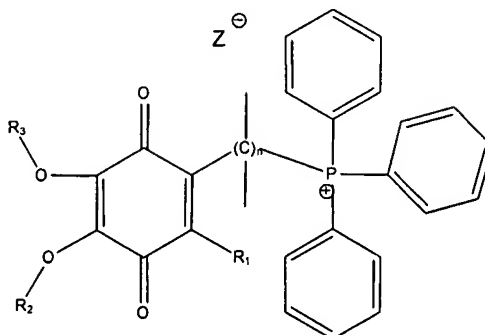
I

or its quinol form, wherein R_1 , R_2 , and R_3 , are the same or different and are selected from C_1 to C_5 alkyl, substituted C_1 to C_5 alkyl and H, and wherein n is an integer from 2 to 20, and wherein Z is a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the compound, the method comprising formation of the compound from triphenylphosphonium without a reaction solvent.

115. (New) The method of claim 114 wherein each C of $(C)_n$ is saturated.

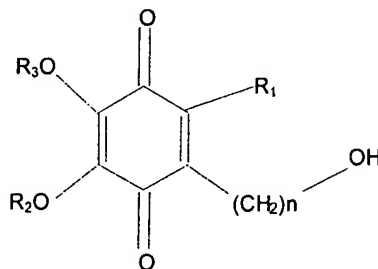
116. (New) The method of claim 114 wherein the compound has a partition coefficient in octanol:water of less than about 20.

117. (New) A method for synthesizing an antioxidant compound of the formula I



I

or its quinol form, wherein R_1 , R_2 , and R_3 , are the same or different and are selected from C_1 to C_5 alkyl, substituted C_1 to C_5 alkyl and H, and wherein n is an integer from 2 to 20, and wherein Z is a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the compound, the method comprising a reaction of a reactant compound of the formula IV



IV

or its quinol form in the presence of Ph_3PHX and Ph_3P , where X is a halogen atom.

118. (New) The method of claim 117 wherein the halogen is selected from the group consisting of bromine, iodine and chlorine.

119. (New) The method of claim 117 wherein the halogen is bromine.

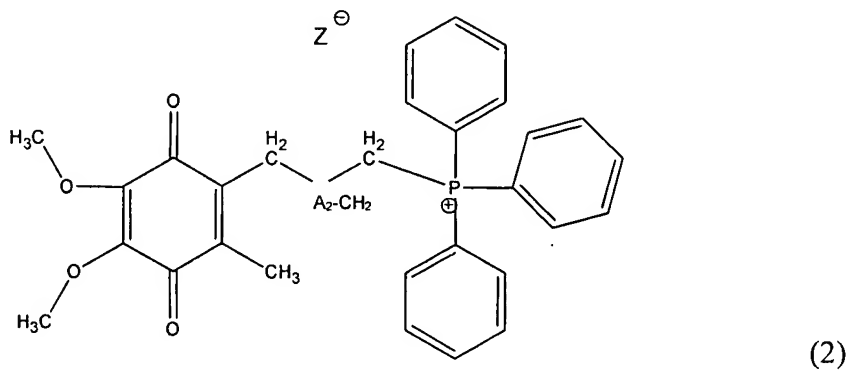
120. (New) The method of claim 117 wherein n is an integer that is selected from the group consisting of 2, 3, 4 and 5.

121. (New) The method of claim 117 wherein the reaction is maintained at a temperature below which significant amounts of R_2PPh_3 or R_3PPh_3 are not formed by ether cleavage.

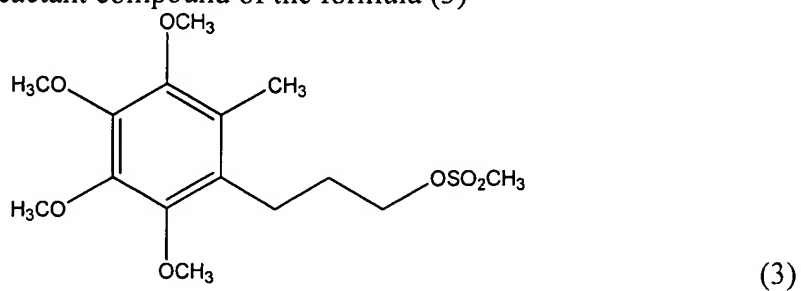
122. (New) The method of claim 117 wherein the reaction is kept below $80^{\circ}C$.

123. (New) The method of claim 117 which comprises the reaction without a reaction solvent.

124. (New) A method for synthesizing an antioxidant compound of the formula (2)



or its quinol form, wherein Z is a salt forming anion that is not a bromide anion or a nitrate anion and does not exhibit reactivity against the compound, the method comprising a reaction of a reactant compound of the formula (3)



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Preliminary Amendment

in the presence of Ph_3P and X, where X comprises a halogen atom.

125. (New) The method of claim 124 wherein the halogen is selected from the group consisting of bromine, iodine and chlorine.

126. (New) The method of claim 124 wherein the halogen is bromine.

127. (New) The method of claim 124 which comprises formation of the antioxidant compound from triphenylphosphonium without a reaction solvent.